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(54) Title: ANGIOSTATIC AGENTS AND COMPOSITIONS FOR CONTROLLING OCULAR HYPERTENSION

(57) Abstract

Compositions of angiostatic agents for treating GLC1A glaucoma and methods for their use are disclosed.

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5 ANGIOSTATIC AGENTS AND COMPOSITIONS FOR CONTROLLING OCULAR HYPERTENSION

This is a continuation-in-part of an application entitled "Angiostatic Steroids and Methods and Compositions for Controlling Ocular Hypertension" filed on December 15, 1997, which is 10 continuation of Serial No. 08/643,387 filed May 6, 1996 (issuing December 16, 1997, Patent No. 5,698,545), which is a continuation of Serial No. 08/349,342 filed December 2, 1994, which is a continuation of U. S. Patent No. 5,371,078 issued December 6, 1994, which is a continuation-in-part of Serial No. 07/559,123 filed July 27, 1990, which is a continuation-in-part of Serial No. 07/419,226 filed October 10, 1989, which is a continuation of Serial No. 07/264,918 filed October 15 31, 1988 (U.S. Patent No. 4,876,250).

Background of the InventionField of the Invention

20 This invention is directed to the use of angiostatic agents for treating glaucoma or ocular hypertension resulting from altered expression of the GLC1A gene (hereinafter GLC1A or 1q glaucoma) in an individual.

Description of Related Art

The glaucomas are a heterogeneous group of optic neuropathies characterized by 30 cupping of the optic nerve head, thinning of the retinal nerve fiber layer due to loss of retinal ganglion cells, and specific pathognomonic changes in visual fields. Elevated intraocular pressure (IOP) is a very important risk factor for the development of most common forms of glaucoma (Sommer A, et al., "Relationship Between Intraocular Pressure and Primary Open Angle Glaucoma Among White and Black Americans," *Arch. Ophthalmol.*, 109:1090-1095, (1991)).

A family history of glaucoma also is an important risk factor for the development of 35 glaucoma. It appears that a significant portion of glaucoma is inherited (or at least the risk for developing glaucoma is inherited) although it is often difficult to establish clear inheritance patterns for most of the glaucomas because of the disease onset late in life and the slowly progressive clinical manifestations of the disease. Despite these problems, a number of families with heritable forms of glaucoma have been identified and these families have been used to map

5 a variety of glaucoma genes (Sheffield, et al., "Genetic Linkage of Familial Open Angle Glaucoma to Chromosome 1q21-q31," *Nature Genetics*, 4:47-50 (1993); Sarfarazi, et al., "Assignment of a Locus (GLC3A) for Primary Congenital Glaucoma (Buphthalmos) to 2p21 and Evidence for Genetic Heterogeneity," *Genomics*, 30:171-177 (1995); Akarsu, et al., "A Second Locus (GLC3B) for Primary Congenital Glaucoma (Buphthalmos) Maps to the 1p36 Region," *Human Molecular Genetics*, 5(8):1199-1203 (1996); Stoilova, et al., "Localization of a Locus (GLC1B) for Adult-Onset Primary Open Angle Glaucoma to the 2cen-q13 Region," *Genomics*, 36:142-150 (1996); Wirtz, et al., "Mapping a Gene for Adult-Onset Primary Open-Angle Glaucoma to Chromosome 3q," *Am. J. Hum. Genet.*, 60:296-304 (1997); Andersen, et al., "A Gene Responsible for the Pigment Dispersion Syndrome Maps to Chromosome 7q35-q36," *Arch. Ophthalmol.*, 115:384-388 (1997). The first glaucoma gene mapped (GLC1A) was in a large family with autosomal dominant inherited juvenile glaucoma (JG). This disease is characterized by an early disease onset (late teens to early 20s), relatively high IOPs, and general resistance to conventional pharmacological IOP lowering therapy. The GLC1A gene was mapped by positional cloning and linkage analysis to chromosome 1q22-q25 (Sheffield et al, *Id.*), and a number of other groups have confirmed the 1q

10 location of this juvenile glaucoma gene (Richards, et al., "Mapping of a Gene for Autosomal Dominant Juvenile-Onset Open-Angle Glaucoma to Chromosome 1q," *Am. J. Hum. Genet.*, 54:62-70 (1994); Morissette, et al., "A Common Gene for Juvenile and Adult-Onset Primary Open-Angle Glaucomas Confined on Chromosome 1q," *Am. J. Hum. Genet.*, 56:1431-1442 (1995); Wiggs, et al., "Genetic Linkage of Autosomal Dominant Juvenile Glaucoma to 1q21-q31 in Three

15 Affected Pedigrees," *Genomics*, 21:299-303 (1994); Meyer, et al., "Age-Dependent Penetrance and Mapping of the Locus for Juvenile and Early-Onset Open-Angle Glaucoma on Chromosome 1q (GLC1A) in a French Family," *Hum. Genet.*, 98:567-571 (1996); Graff, et al., "Confirmation of Linkage to 1q21-31 in a Danish Autosomal Dominant Juvenile-Onset Glaucoma Family and Evidence of Genetic Heterogeneity," *Hum. Genet.*, 96:285-289 (1995). Glaucoma due to the

20 GLC1A gene is often referred to as 1q glaucoma.

35 The GLC1A gene was identified as encoding a 57 kD protein expressed in the trabecular meshwork (TM) (Stone, et al., "Identification of a Gene That Causes Primary Open Angle Glaucoma," *Science*, 275:668-670 (1997). The expression of the GLC1A gene, and the encoded TM protein, is up-regulated by glucocorticoids (Polansky, et al., "Eicosanoid Production and Glucocorticoid Regulatory Mechanisms in Cultured Human Trabecular Meshwork Cells," *The*

5 *Ocular Effects of Prostaglandins and Other Eicosanoids*, pp. 113-138 (1989); Polansky, et al., "In Vitro Correlates of Glucocorticoid Effects on Intraocular Pressure," *Glaucoma Update IV* (1991); and Polansky, et al., "Cellular Pharmacology and Molecular Biology of the Trabecular Meshwork Inducible Glucocorticoid Response Gene Product," *Ophthalmologica*, 211:126-139 (1997)). This TM protein is also known as TIGR (trabecular meshwork inducible glucocorticoid response) (Polansky, *Id.*). The glucocorticoid-induction of this TM protein has been suggested to be involved 10 in the generation of glucocorticoid-induced ocular hypertension and glaucoma (Polansky, *Id.*).

The GLC1A gene is expressed in other ocular tissues such as the ciliary epithelium (Ortego, et al., "Cloning and Characterization of Subtracted cDNAs from a Human Ciliary Body Library Encoding TIGR, a Protein Involved in Juvenile Open Angle Glaucoma with Homology to Myosin and Olfactomedin," *FEBS Letters*, 413:349-353 (1997)) and the retina (Kubota, et al., "A Novel Myosin-like Protein (Myocilin) Expressed in the Connecting Cilium of the Photoreceptor: Molecular Cloning, Tissue Expression, and Chromosomal Mapping," *Genomics*, 41:360-369 (1997)). The gene is referred to by several names including GLC1A (Sheffield, *supra*; Sunden, et al., "Fine Mapping of the Autosomal Dominant Juvenile Open Angle Glaucoma (GLC1A) Region and Evaluation of Candidate Genes," *Genome Research*, 6:862-869 (1996); Stone, et al., *supra*), TIGR (Polansky *supra*; Ortego, *supra*), and myocilin (Kubota, *supra*). Mutations GLC1A are not only responsible for juvenile glaucoma, but also a significant subset of adult onset primary open angle glaucoma (Stone, et al., *supra*; Adam, et al., "Recurrent Mutations in a Single Exon 20 Encoding the Evolutionarily Conserved Olfactomedin-Homology Domain of TIGR in Familial Open-Angle Glaucoma," *Human Molecular Genetics*, 6(12):2091-2097 (1997)). The 1q glaucoma gene (GLC1A, TIGR) is the subject of Nguyen, et al., U.S. Patent No. 5,606,043, issued February 25, 25 1997.

30 Glucocorticoids have been associated with the development of ocular hypertension and primary open angle glaucoma (Kass, et al., "Corticosteroid-Induced Glaucoma, In Ritch, R., Shields, M. B., Krupin, T. (eds.)," *The Glaucomas*, The C. V. Mosby Company, St. Louis, MO, pp. 1161-1168 (1989); DeSantis, et al., "Dexamethasone-Induction of Ocular Hypertension in the Primate, ARVO Abstracts. *Invest. Ophthalmol. Vis. Sci.*, 31(Suppl.):99 (1990); Knepper, et al., "Intraocular Pressure 35 and Glycosaminoglycan Distribution in the Rabbit Eye: Effect of Age and Dexamethasone," *Exp. Eye Res.*, 27: 567-575 (1978); Francois, et al., "Ultrastructural and Morphometric Study of

5 Corticosteroid Glaucoma in Rabbits, *Ophthalmic Res.*, 16:168-178 (1984); Lorenzetti, O. J., "Effects
of Corticosteroids on Ocular Dynamics in Rabbits," *J. Pharmacol. Exp. Therap.*, 175:763-772 (1970);
and Zhan, et al., "Steroid Glaucoma: Corticosteroid-Induced Ocular Hypertension in Cats," *Exp. Eye
Res.*, 54:211-218 (1992)). Glaucoma patients have also been reported to have higher levels of the
endogenous glucocorticoid, cortisol (Rozsival, et al., "Aqueous Humour and Plasma Cortisol Levels
10 in Glaucoma and Cataract Patients," *Current Eye Research*, 1:391-396 (1981); Ray, et al., "Plasma
Cortisol in Glaucoma," *Ann. Ophthalmol.*, 9:1151-1154 (1977); and Schwartz, et al., "Increased
Plasma Free Cortisol in Ocular Hypertension and Open Angle Glaucoma," *Arch. Ophthalmol.*,
105:1060-1065 (1987)).

15 It is known that trabecular meshwork cells have glucocorticoid receptors and that
glucocorticoid binding with these receptors causes a change in trabecular meshwork cell gene
expression. Known manifestations of this change include a reorganization of the cytoskeleton
(Wilson, et al., "Dexamethasone Induced Ultrastructural Changes in Cultured Human Trabecular
Meshwork Cells, *Cur. Eye Res.*, 12:783-793 (1993), and Clark, et al., "Glucocorticoid-Induced
20 Formation of Cross-Linked Actin Networks in Cultured Human Trabecular Meshwork Cells," *Invest.
Ophthalmol. Vis. Sci.*, 35:281-294 (1994)) and increased deposition of the extracellular matrix
material in trabecular meshwork cells. As a result, the trabecular meshwork becomes "clogged" and
unable to perform one of its most critical functions, that is, serving as a gateway for aqueous humor
25 flow from the anterior chamber of the eye. When the aqueous humor flow out of the eye via the
trabecular meshwork is diminished, the intraocular pressure of the eye rises. If this state of elevated
intraocular pressure is maintained or frequently occurs, the optic nerve head can be damaged
resulting in the loss of visual field. Loss of visual field is the hallmark symptom associated with
30 glaucoma.

30 Endogenous glucocorticoids may be responsible for producing the changes in the trabecular
meshwork that lead to ocular hypertension and glaucoma.

35 In summary, the GLC1A gene product can lead to the development of ocular hypertension
and glaucoma in one of two ways: (1) mutations in GLC1A are responsible for most forms of
juvenile glaucoma and a subset of adult onset POAG or (2) exposure of some individuals to
glucocorticoids leads to increased GLC1A expression in the TM which causes increased aqueous

5 humor outflow resistance and the development of ocular hypertension. The precise mechanism(s) responsible for GLC1A effects on IOP are currently unknown.

Steroids functioning to inhibit angiogenesis in the presence of heparin or specific heparin fragments are disclosed in Crum, et al., "A New Class of Steroids Inhibits Angiogenesis in the Presence of Heparin or a Heparin Fragment," *Science*, 230:1375-1378 (December 20, 1985). The authors refer to such steroids as "angiostatic" steroids. Included within the new class of steroids found to be angiostatic are the dihydro and tetrahydro metabolites of cortisol and cortexolone. In a follow-up study directed to testing a hypothesis as to the mechanism by which the steroids inhibit angiogenesis, it was shown that heparin/angiostatic steroid compositions cause dissolution of the basement membrane scaffolding to which anchorage dependent endothelia are attached resulting in capillary involution; see, Ingber, et al., "A Possible Mechanism for Inhibition of Angiogenesis by Angiostatic Steroids: Induction of Capillary Basement Membrane Dissolution," *Endocrinology*, 119:1768-1775 (1986).

20 A group of tetrahydro steroids useful in inhibiting angiogenesis is disclosed in International Patent Application No. PCT/US86/02189, Aristoff, et al., (The Upjohn Company). The compounds are disclosed for use in treating head trauma, spinal trauma, septic or traumatic shock, stroke and hemorrhage shock. In addition, the patent application discusses the utility of these compounds in embryo implantation and in the treatment of cancer, arthritis and arteriosclerosis. The compounds are not disclosed for ophthalmic use.

30 Tetrahydrocortisol (THF) has been disclosed for its use in lowering the intraocular pressure (IOP) of rabbits made hypertensive with dexamethasone alone, or with dexamethasone/5-beta-dihydrocortisol; see Southren, et al., "Intraocular Hypotensive Effect of a Topically Applied Cortisol Metabolite: 3-alpha, 5-beta-tetrahydrocortisol," *Investigative Ophthalmology and Visual Science*, 28 (May, 1987). The authors suggest THF may be useful as an antiglaucoma agent. In U.S. Patent No. 4,863,912, issued to Southren et al. on September 5, 1989, pharmaceutical compositions containing THF and a method for using these compositions to control intraocular pressure are disclosed. THF has been disclosed as an angiostatic steroid in Folkman, et al., "Angiostatic Steroids," *Ann. Surg.*, 206(3) (1987) wherein it is suggested angiostatic steroids may have potential use for diseases dominated by abnormal

5 neovascularization, including diabetic retinopathy, neovascular glaucoma and retrobulbar fibroplasia.

Summary of the Invention

10 Angiostatic steroids and their pharmaceutical formulations are useful for treating GLC1A glaucoma. The invention is also directed to methods for controlling GLC1A glaucoma using angiostatic steroids.

Detailed Description of Preferred Embodiments

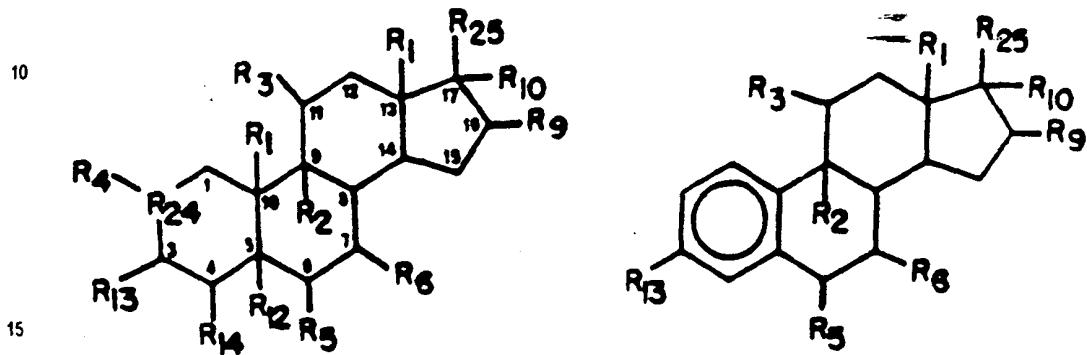
15 Agents which alter the expression of GLC1A in the glaucomatous eye are expected to lower IOP and thereby prevent or inhibit the glaucomatous optic neuropathy which is being driven by elevated IOP. Glucocorticoids upregulate GLC1A expression in the TM of certain individuals. There have been several reports of elevated levels of the natural glucocorticid cortisol in the 20 aqueous humor and plasma of glaucoma patients (Schwartz, et al., *supra*; Rozsival, et al., *supra*). In addition, certain mutations in GLC1A may alter the expression of GLC1A in the TM tissue of 1q glaucoma patients. Unexpectedly, it has been discovered that angiostatic agents inhibit the expression of GLC1A in cultured human TM cells and lower elevated IOP in certain animal models 25 of ocular hypertension. The compounds thereby prevent the expression of GLC1A and the subsequent development of ocular hypertension.

30 The development of blood vessels for the purpose of sustaining viable tissue is known as angiogenesis. Agents which inhibit angiogenesis are known by a variety of terms such as angiostatic, angiolytic or angiotropic agents. For purposes of this specification, the term "angiostatic agent" means compounds which can be used to inhibit angiogenesis.

35 The specific angiostatic agents of the present invention are steroids or steroid metabolites. For purposes herein, the term "angiostatic steroids" means steroids and steroid metabolites which inhibit angiogenesis. The present invention is based on the finding that angiostatic steroids can be used for the control of ocular hypertension. In particular, the agents can be used for the treatment of GLC1A glaucoma.

5

Preferred angiostatic steroids of the present invention have the following formula:



Structure [A]

Structure [B]

20

wherein R₁ is H, β -CH₃ or β -C₂H₅;

R₂ is F, C₉-C₁₁ double bond, C₉-C₁₁ epoxy, H or Cl;

R₃ is H, OR₂₆, OC(=O)R₂₇, halogen, C₉-C₁₁ double bond, C₉-C₁₁ epoxy, =O, -OH, -O-alkyl(C₁-C₁₂), -OC(=O)alkyl(C₁-C₁₂), -OC(=O)ARYL, -OC(=O)N(R)₂ or

25 -OC(=O)OR₇, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C₁-C₄)alkyl groups, or ARYL is -(CH₂)_f-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C₁-C₃), alkoxy(C₁-C₃), thioalkoxy-(C₁-C₃), Cl₃C-, F₃C-, -NH₂ and -NHCOCH₃ and R is hydrogen, alkyl (C₁-C₄), or phenyl and each R can be the same or different, and R₇ is ARYL as herein defined, or alkyl(C₁-C₁₂);

30 R₄ is H, CH₃, Cl or F;

R₅ is H, OH, F, Cl, Br, CH₃, phenyl, vinyl or allyl;

R₆ is H or CH₃;

R₉ is CH₂CH₂OR₂₆, CH₂CH₂OC(=O)R₂₇, H, OH, CH₃, F, =CH₂, CH₂C(=O)OR₂₈, OR₂₆, O(C=O)R₂₇

35 or O(C=O)CH₂(C=O)OR₂₆

R₁₀ is -C≡CH, -CH=CH₂, halogen, CN, N₃, OR₂₆, OC(=O)R₂₇, H, OH, CH₃ or R₁₀ forms a second

5 bond between positions C-16 and C-17;
R₁₂ is H or forms a double bond with R₁ or R₁₄;
R₁₃ is halogen, OR₂₆, OC(=O)R₂₇, NH₂, NHR₂₆, NHC(=O)R₂₇, N(R₂₆)₂, NC(=O)R₂₇, N₃, H, -OH, =O, -O-P(=O)(OH)₂, or -O-C(=O)-(CH₂)_tCOOH where t is an integer from 2 to 6;
R₁₄ is H or forms a double bond with R₁₂;

10 R₁₅ is H, =O or -OH;
and R₂₃ with R₁₀ forms a cyclic phosphate;
wherein R₉ and R₁₅ have the meaning defined above;
or wherein R₂₃ is -OH, O-C(=O)-R₁₁, -OP(O)-(OH)₂, or -O-C(=O)-(CH₂)_tCOOH wherein t is an integer from 2 to 6; and R₁₁ is -Y-(CH₂)_n-X-(CH₂)_m-SO₃H,

15 -Y'-(CH₂)_p-X'-(CH₂)_q-NR₁₆R₁₇ or -Z(CH₂)_rQ,
wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond, -CON(R₁₈)-, -N(R₁₈)CO-, -O-, -S-, -S(O)-, or -S(O₂)-; R₁₈ is hydrogen or alkyl (C₁-C₄); each of R₁₆ and R₁₇ is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R₁₆ and R₁₇ taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;
Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:
(1) -R₁₉-CH₂COOH wherein R₁₉ is -S-, -S(O)-, -S(O)₂-, -SO₂N(R₂₀)-, or N(R₂₀)SO₂-; and
25 R₂₀ is hydrogen or lower alkyl-(C₁-C₄); with the proviso that the total number of carbon atoms in R₂₀ and (CH₂)_r is not greater than 10; or
(2) -CO-COOH; or
(3) CON(R₂₁)CH(R₂₂)COOH wherein R₂₁ is H and R₂₂ is H, CH₃, -CH₂COOH, -CH₂CH₂COOH, -CH₂OH, -CH₂SH, -CH₂CH₂SCH₃, or
30 -CH₂Ph-OH wherein Ph-OH is p-hydroxyphenyl;
or R₂₁ is CH₃ and R₂₂ is H;
or R₂₁ and R₂₂ taken together are -CH₂CH₂CH₂-;
or -N(R₂₁)CH(R₂₂)COOH taken together is -NHCH₂CONHCH₂COOH; and pharmaceutically acceptable salts thereof;

35 with the proviso that if R₂₃ is a phosphate, it must form a cyclic phosphate, with R₁₀ when R₁₃ is =O, except for the compound wherein R₁ is β -CH₃, R₂ and R₃ taken together form a double bond

5 between positions 9 and 11, R₄ and R₆ are hydrogen, R₁₂ and R₁₄ taken together form a double bond between positions 4 and 5, R₅ is α -F, R₉ is β -CH₃, R₁₀ is α -OH, R₁₃ and R₁₅ are =O and R₂₃ is -OP(O)-(OH)₂.

R₂₄ = C, C₁-C₂ double bond, O;

R₂₅ = C(R₁₅)CH₂-R₂₃, OH, OR₂₆, OC(=O)R₂₇, R₂₆, COOH, C(=O)OR₂₆,

10 CHOCH₂OH, CHOCH₂OR₂₆, CHOCH₂OC(=O)R₂₇, CH₂CH₂OH,

CH₂CH₂OR₂₆, CH₂CH₂OC(=O)R₂₇, CH₂CN, CH₂N₃, CH₂NH₂,

CH₂NHR₂₆, CH₂N(R₂₆)₂, CH₂OH, CH₂OR₂₆, CH₂O(C=O)R₂₇, CH₂O(P=O)(OH)₂,

CH₂O(P=O)(OR₂₆)₂, CH₂SH, CH₂S-R₂₆, CH₂SC(=O)R₂₇,

CH₂NC(=O)R₂₇, C(=O)CHR₂₈OH, C(=O)CHR₂₈OR₂₆, C(=O)CHR₂₈OC(=O)R₂₇ or

15 R₁₀ and R₂₅ taken together may be =C(R₂₈)₂, that is, an optionally

alkyl substituted methylene group;

wherein R₂₆ = C₁-C₆ (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl);

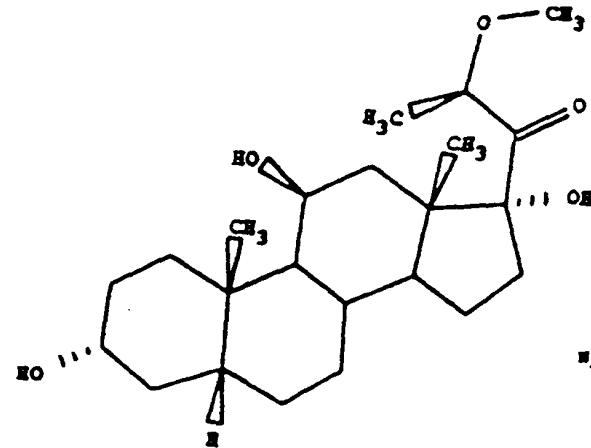
R₂₇ = R₂₆ + OR₂₆; R₂₈ = H, C₁-C₆ (alkyl, branched alkyl, cycloalkyl).

20 Unless specified otherwise, all substituent groups attached to the cyclopentanophenanthrene moiety of Structures [A] and [B] may be in either the alpha or beta position. Additionally, the above structures include all pharmaceutically acceptable salts of the angiostatic steroids.

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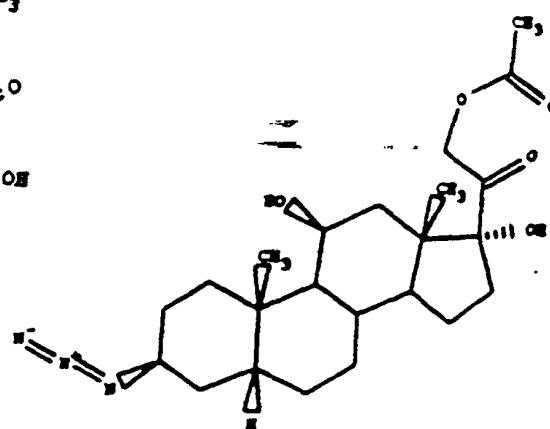
Preferred angiostatic steroids are:

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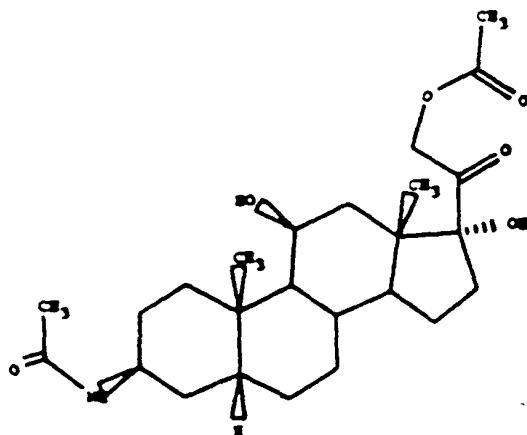
21-METHYL-5 β -PREGNAN-3 α ,11 β ,17 α ,
21-TETROL-20-ONE 21-METHYL ETHER



20

3 β -AZIDO-5 β -PREGNAN-11 β ,
17 α ,21-TRIOL-20-ONE-21-ACETATE

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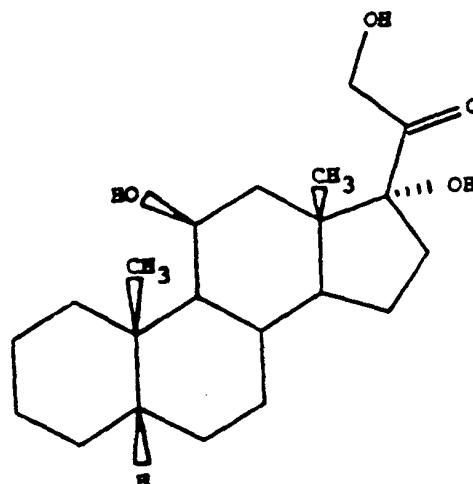


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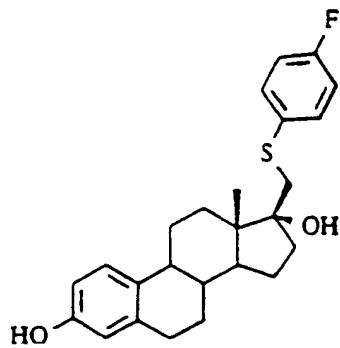


3 β -ACETAMIDO-5 β -PREGNAN-
11 β ,17 α ,21-TRIOL-20-ONE
21-ACETATE

5 β -PREGNAN-11 β ,17 α ,21-TRIOL-20-ONE

5

10



15 17-((4-FLUOROPHENOXY)METHYL-
1,3,5-ESTRATRIEN-3,17-DIOL

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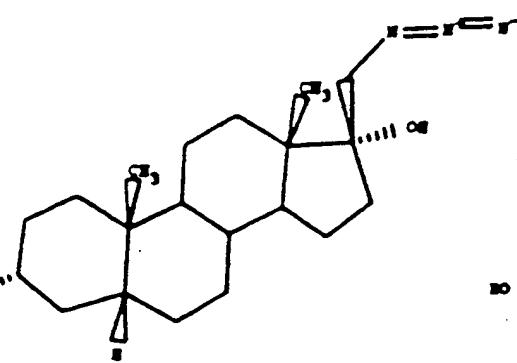
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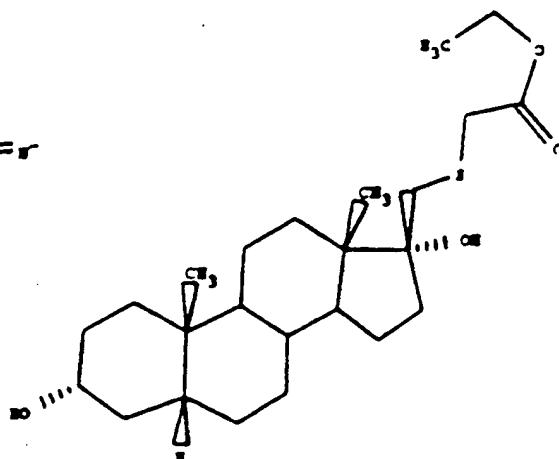
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20-AZIDO-21-NOR-5 β -PREGNAN-3 α ,
17 α -DIOL



20-(CARBETHOXYMETHYL)THIO-21-NOR-5 β -
PREGNAN-3 α , 17 α -DIOL

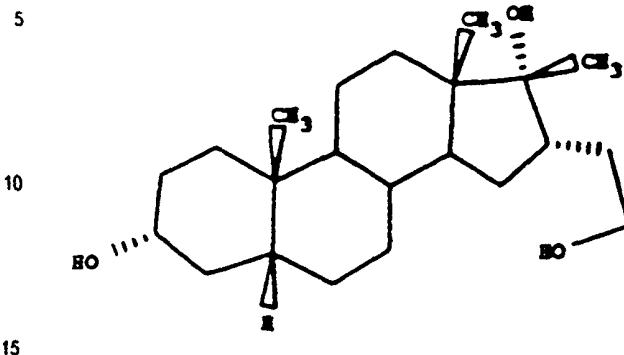


20-(4-FLUOROPHENYL)THIO-21-NOR-
PREGNAN-3 α ,17 α -DIOL

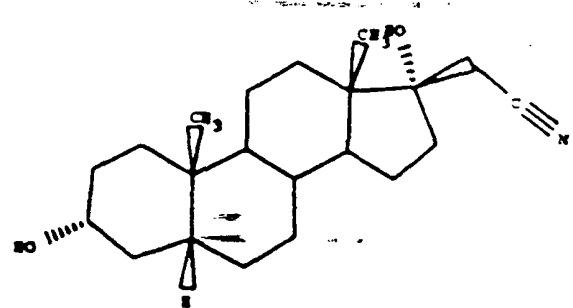
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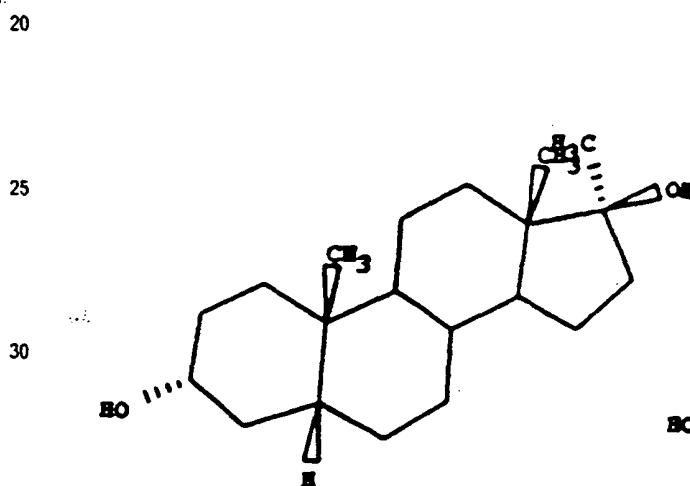
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17 α -DIOL-3-ACETATE



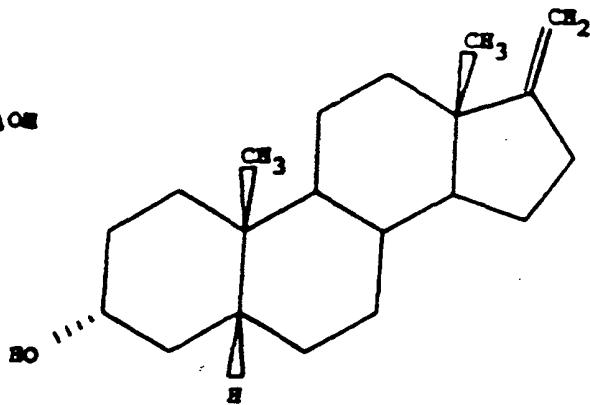
16 α -(2-HYDROXYETHYL)-17 β -METHYL-
5 β -ANDROSTAN-3 α ,17 α -DIOL



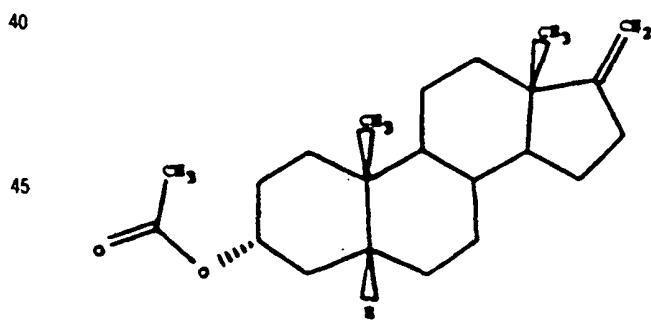
20-CYANO-21-NOR-5 β -PREGNAN-3 α ,17 α -
DIOL



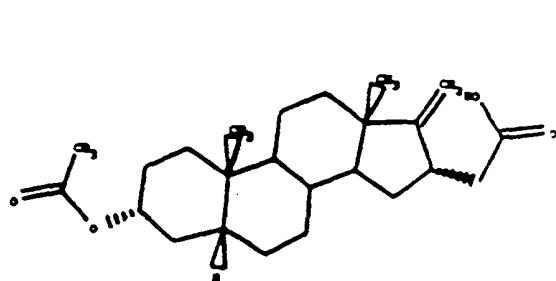
17 α -METHYL-5 β -ANDROSTAN-
3 α ,17 β -DIOL



21-NOR-5 β -PREGN-17(20)-EN-3 α -OL



21-NOR-5 β -PREGN-17(20)-EN-
3 α -OL-3-ACETATE

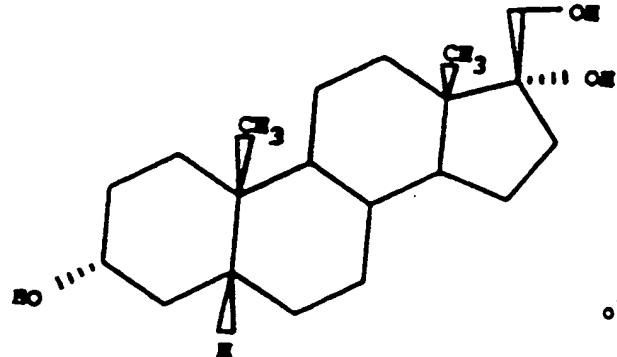


21-NOR-5 β -PREGN-17(20)-EN-3 α -OL-
16-ACETIC ACID-3-ACETATE

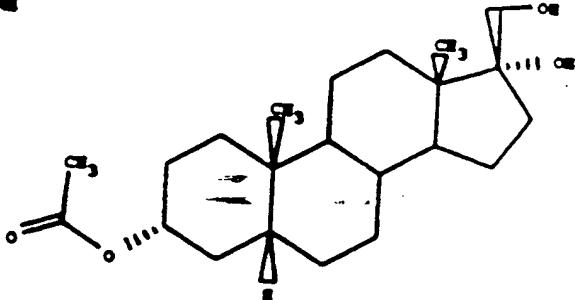
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21-NOR-5 β -PREGNAN-3 α ,17 α ,20-TRIOL



21-NOR-5 β -PREGNAN-3 α ,17 α ,20-TRIOL-3-ACETATE

5

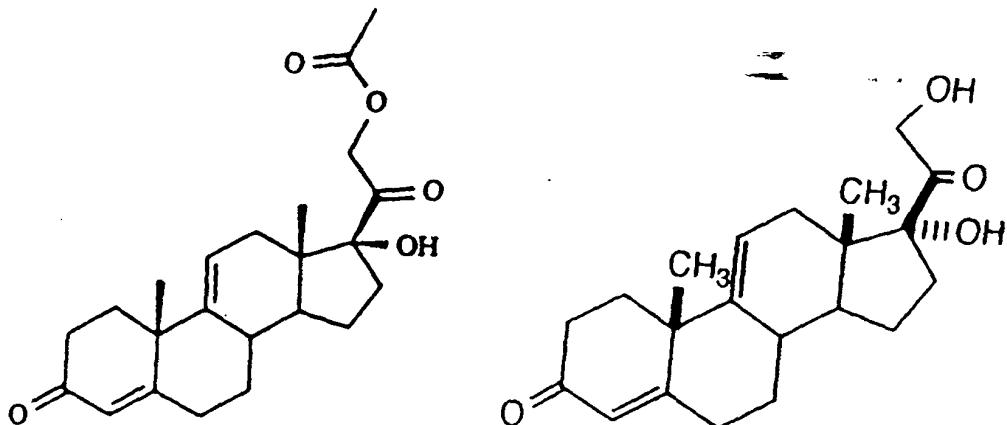
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4,9(11)-PREGNADIEN-17 α ,21-DIOL-3,20-DIONE-21-ACETATE4,9(11)-PREGNADIEN-17 α ,21-DIOL-3,20-DIONE

The more preferred compounds are 21-methyl-5 β -pregnan-3 α , 11 β , 17 α ,21-tetrol 20-one-21-methyl ether; 3 β -azido-21-acetoxy-5 β -pregnan-11 β , 17 α -diol-20-one; 3 β -acetamido-21-acetoxy-5 β -pregnan-11 β , 17 α -diol-20-one; and 5 β -pregnan-11 β , 17 α , 21-triol-20-one. The most preferred compounds are 4,9(11)-pregnadien-17 α ,21-diol-3,20-dione-21-acetate and 4,9(11)-pregnadien-17 α ,21-diol-3,20-dione.

The angiostatic steroids of the present invention may be incorporated in various formulations for delivery to the eye. For example, topical formulations can be used and can include ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic ointment formulations, an angiostatic steroid is combined with a preservative in an appropriate vehicle, such as mineral oil, liquid lanolin or white petrolatum.

5 Sterile ophthalmic gel formulations comprising the angiostatic steroids of the present invention can be prepared by suspending an angiostatic steroid in a hydrophilic base prepared from a combination of, for example, Carbopol-940 (a carboxyvinyl polymer available from the B.F. Goodrich Company) according to published formulations for analogous ophthalmic preparations. Preservatives and tonicity agents may also be incorporated in such gel formulations.

10

The specific type of formulations selected will depend on various factors, such as the angiostatic steroid or its salt being used, and the dosage frequency. Topical ophthalmic aqueous solutions, suspensions, ointments and gels are the preferred dosage forms. The angiostatic steroid will normally be contained in these formulations in an amount of from about 0.005 to about 15 5.0 weight percent (wt.%). Preferable concentrations range from about 0.05 to about 2.0 wt.%. Thus, for topical administration, these formulations are delivered to the surface of the eye one to four times per day, depending upon the routine discretion of the skilled clinician.

20 The following examples illustrate formulations and synthesis of compounds of the present invention, but are in no way limiting.

Example 1

| | <u>Component</u> | <u>wt.%</u> |
|----|-----------------------|-------------|
| 25 | Angiostatic Steroid | 0.005-5.0 |
| | Tyloxapol | 0.01-0.05 |
| | HPMC | 0.5 |
| | Benzalkonium Chloride | 0.01 |
| | Sodium Chloride | 0.8 |
| 30 | Edetate Disodium | 0.01 |
| | NaOH/HCl | q.s. pH 7.4 |
| | Purified Water | q.s. 100 mL |

5

Example 2

| | <u>Component</u> | <u>wt.%</u> |
|----|---|-------------|
| | 4,9(11)-pregnadien-17 α ,21-diol-3,20-dione-21-acetate | 1.0 |
| | Mannitol | 2.40 |
| 10 | Carbopol 974P | 0.50 |
| | Polysorbate 80 | 0.05 |
| | Benzalkonium Chloride | 0.01 |
| | Sodium Chloride | 0.4 |
| | Eddetate Disodium | 0.01 |
| 15 | NaOH/HCl | q.s. pH 7.4 |
| | Purified Water | q.s. 100 mL |

5

Example 3Preparation of 5 β -Pregnan-11 β , 17 α , 21-triol-20-oneTetrahydrocortisol-F-21-t-butyldiphenylsilyl ether (PS03842)

10 A solution of 4.75 g (17.3 mmol) of t-butyldiphenylchlorosilane in 5 mL of dry DMF was added dropwise to a stirred solution of 5.7 g (15.6 mmol) of tetrahydrocortisol-F (Steraloids No. P9050) and 2.3 g (19 mmol) of 4-dimethylaminopyridine (DMAP) in 30 mL of dry DMF, under N₂, at -25 to -30°C (maintained with CO₂ - MeCN). After a further 20 min at -30°C, the mixture was allowed to warm to 23°C overnight.

15

The mixture was partitioned between ether and water, and the organic solution was washed with brine, dried (MgSO₄), filtered and concentrated to give 10.7 g of a white foam.

20 This material was purified by flash column chromatography (400 g silica; 62.5 to 70% ether/hexane). The 3-siloxy isomer eluted first, followed by mixed fractions, followed by the title compound. The concentrated mixed fractions (4.0 g) were chromatographed on the same column with 35% ethyl acetate/hexane. The total yield of the 3-siloxy isomer was 0.42 g (5%), and of the title compound, 5.05 g (53.5%). Continued elution with 25% MeOH/EtOAc allowed recovery of unreacted tetrahydrocortisol-F.

25

PS03842

30 NMR (200 MHz ¹H) (CDCl₃): δ0.63 (s, 3H, Me-18); 1.11 (s, 9H, t-Bu); 1.12 (s, 3H, Me-19); 2.57 (t, J=13, 1H, H-8); 2.6 (s, 1H, OH-17); 3.63 (sept, J=2.5, 1H, H-3); 4.15 (br s, 1H, H-11); 4.37 and 4.75 (AB, J=20, 2H, H-21); 7.4 (m, 6H) and 7.7 (m, 4H) (Ph₂).

35 NMR (200 MHz ¹H) (DMSO-d₆): δ0.64 (s, 3H, Me-18); 1.02 (s, 9H, t-Bu); 1.07 (s, 3H, Me-19); 2.50 (t, J=13, 1H, H-8); 3.37 (m, 1H, H-3); 3.94 (d, J=2, 1H, OH-11); 4.00 (br s, 1H, H-11); 4.42 (d, J=5, 1H, OH-3); 4.38 and 4.83 (AB, J=20, 2H, H-21); 5.11 (s, 1H, OH-17); 7.45 (m, 6H) and 7.6 (m, 4H) (Ph₂).

40 NMR (50.3 - MHz ¹³C) (CDCl₃): 17.4 (C-18); 19.3 (C-16); 23.7 (C-15); 26.3 (C-7); 26.6 (C-19); 26.8 (Me₃C); 27.2 (C-6); 30.9 (C-2); 31.5 (C-8); 34.1 (Me₃C); 34.8 (C-10); 35.2 (C-1); 36.2 (C-4);

5 39.7 (C-13); 43.5 (C-5); 44.3 (C-9); 47.4 (C-12); 52.1 (C-14); 67.8 (C-11); 68.9 (C-21); 71.7 (C-3);
89.8 (C-14); 127.8, 129.8, 132.8, 132.9, 135.7, 135.8 (diastereotopic Ph₂); 208.8 (C-20).

Underlined resonances showed inversion in the APT experiment. Assignments: E. Breitmaier, W. Voelter "Carbon-13 NMR Spectroscopy," 3d ed., VCH, 1987; pp. 345-348.

10 IR (KBr) 3460, 2930, 2860, 1720, 1428, 1136, 1113, 1070, 1039, 703 cm⁻¹.

This compound did not show a sharp melting point but turned to a foam at 80-100°C. Numerous attempts at recrystallization failed.

15 5β-Pregnan-11β, 17α, 21-triol-20-one

A solution of PSO3842 (0.91 g, 1.50 mmol) and thiocarbonyl diimidazole (1.05 g, 5.9 mmol) in 8 mL of anhydrous dioxane was refluxed under N₂ for 3.5 h. The cooled solution was partitioned between ether and water and the organic solution was washed with brine, dried (MgSO₄), filtered and concentrated. The residue was chromatographed (120 g SiO₂, 35% EtOAc/hexane) giving 20 0.86 g (80%) of the imidazolyl thioester.

A solution of 0.75 g (1.05 mmol) of this compound in 100 mL of anhydrous dioxane was added dropwise over 2.2 h to a rapidly stirred, refluxing solution of 1.6 mL (5.9 mmol) of Bu₃SnH in 100 mL of anhydrous dioxane under N₂. After a further 1 h at reflux, the solution was cooled, concentrated and the residue chromatographed (200 g SiO₂, 9% EtOAc/hexane) giving 0.43 g (70%) of the 3-deoxy-21-silyl ether. This material was dissolved in 20 mL of methanol; Bu₄NF·3H₂O (0.50 g, 1.6 mmol) was added, and the mixture was heated to reflux under N₂ for 4 h. The cooled solution was diluted with 2 volumes of EtOAc, concentrated to 1/4 volume, partitioned (EtOAc/H₂O), and the organic solution was washed with brine, dried (MgSO₄), filtered and concentrated. The residue (0.40 g) was chromatographed (30 g SiO₂, 40% EtOAc/hexane) to give 0.25 g (98%) of an oil.

35 This oil was crystallized (n-BuCl) to afford 0.14 g of the title compound as a white solid, m.p. 167-170°C.

5 IR (KBr): 3413 (br), 2934, 1714, 1455, 1389, 1095, 1035 cm^{-1} .

MS (CI): 351 (M +1).

10 NMR (200 MHz ^1H , DMSO-d₆): δ 0.69 (s, 3H, Me-18); 1.14 (s, 3H, Me-19); 0.8-2.0 (m); 2.5 (t, J=13, 1H, H-8); 3.96 (d, J=2, 1H, OH-11); 4.1 (br s, 1H, H-11); 4.1 and 4.5 (AB, further split by 5 Hz, 2H, H-21); 4.6 (t, J=5, 1H, OH-21); 5.14 (s, 1H, OH-17).

Anal. Calc'd for C₂₁H₃₄O₄: C, 71.96; H, 9.78.

Found: C, 71.69; H, 9.66.

Example 4

Preparation of 21-Methyl-5 β -pregnan-3 α , 11 β , 17 α , 21-tetrol-20-one 21-methyl ether

10 Sodium hydride (60% oil dispersion, 0.10 g, 2.5 mmol) was added to a stirred solution of tetrahydrocortisol-F (0.73 g, 2.0 mmol) and CH₃I (0.60 mL, 9.6 mmol) in 8 mL of anhydrous DMF under N₂. Hydrogen was evolved, and the temperature rose to 35°C. After 1 h, the mixture was diluted with EtOAc, extracted with water (until neutral) and brine, dried (MgSO₄), filtered and concentrated. The residue was chromatographed (70 g SiO₂, 80% EtOAc/hexane) to give 0.17 g
15 of a white solid, MS (Cl) = 395 (M +1). This material was recrystallized (EtOAc-n-BuCl) to afford 0.12 g (16%) of the title compound as a feathery white solid, m.p. 208-213 °C.

IR (KBr): 3530, 3452, 2939, 2868, 1696 (s, CO), 1456, 1366, 1049 cm⁻¹.

20 NMR (200 MHz ¹H, DMSO-d₆): δ 0.74 (s, 3H, Me-18); 1.09 (s, 3H, Me-19); 1.14 (d, J=6.6, 3H, C-21 Me); 0.8-2.0 (m); 2.47 (t, J=13, 1H, H-8); 3.18 (s, 3H, OMe); 3.35 (m, 1H, H-3); 4.00 (d, J=2, 1H, OH-11); 4.07 (br s, 1H, H-11); 4.37 (q, J=6.6, 1H, H-21); 4.43 (d, J=5, 1H, OH-3); 5.16 (s, 1H, OH-17).

25 Anal. Calc'd for C₂₃H₃₈O₅: C, 70.01; H, 9.71.

Found: C, 70.06; H, 9.76.

Example 5

Preparation of 3 β -Azido-21-acetoxy-5 β -pregnan-11 β ,
17 α -diol-20-one

10 A solution of triphenylphosphine (2.6 g, 10 mmol) in 10 mL of toluene was carefully added to a stirred solution of PS03842 (see Example 4) (1.75 g, 2.90 mmol), diphenylphosphoryl azide (2.2 mL, 10.2 mmol) and diethyl azodicarboxylate (1.55 mL, 10 mmol) under N₂, keeping the internal temperature below 35°C (exothermic). The solution was stirred for 1.2 h, then diluted with ether, washed with water and brine, dried (MgSO₄), filtered and concentrated and the residue (9.5 g, oil) chromatographed (175 g SiO₂, 15% EtOAc/hexane) giving 1.83 g of a viscous oil.

15 A solution of 1.73 g of this material and 1.75 g (5.5 mmol) of Bu₄NF-3H₂O in 20 mL of methanol was refluxed under N₂ for 2.5 h. The crude product (1.94 g) was isolated with ethyl acetate and chromatographed (100 g SiO₂, 50% EtOAc/hexane) giving 0.60 g (56%) of a white semisolid.

20 Trituration (4:1 hexane-ether) gave 0.57 g (53%) of a solid.

25 A stirred solution of 0.40 g of this material in 3 mL of dry pyridine was treated with 0.3 mL of acetic anhydride and stirred overnight at 23°C under N₂. The mixture was quenched with 1 mL of methanol, stirred for 15 min, diluted with ether, washed with 1 M aqueous HCl, water (until neutral), brine, dried (MgSO₄), filtered and concentrated. The residue (0.41 g, oil) was chromatographed (35 g SiO₂, 33% EtOAc/hexane) to afford 0.33 g (76%) of the title compound as a white foam, m.p. 80-90°C (dec).

30 IR (KBr): 3505, 2927, 2866, 2103 (vs), 1721 (sh 1730), 1268, 1235 cm⁻¹.

35 NMR (200 MHz ¹H, CDCl₃): δ 0.92 (s, 3H, Me-18); 1.21 (s, 3H, Me-19); 1.0-2.1 (m); 2.17 (s, 3H, Ac); 2.25 (s 1H, OH-17); 2.74 (m, 1H, H-8); 3.97 (br s, 1H, H-3); 4.31 (br s, 1H, H-11); 4.94 (AB, J=17, Δ v=60, 2H, H-21).

35 Anal. Calc'd for C₂₃H₃₅N₃O₅: C, 63.72; H, 8.14; N, 9.69.
Found: C, 63.39; H, 8.18; N, 9.45.

5

Example 6

Preparation of 3 β -Acetamido-21-acetoxy-5 β -pregnan-11 β ,
17 α -diol-20-one

10

A solution of 3 β -azido-21-acetoxy-5 β -pregnan-11 β ,17 α -diol-20-one (0.15 g, 0.35 mmol) in 8 mL of absolute ethanol containing 0.03 g of 10% Pd on C was stirred under H₂ (1 atm) at 23°C for 2 h. The mixture was filtered and concentrated, the residue dissolved in EtOAc, the basic material extracted into 1 M aqueous HCl, liberated (Na₂CO₃), extracted (EtOAc) and the organic extract washed with water (until neutral) and brine, dried (MgSO₄), filtered and concentrated to provide 58 mg of a solid.

This material was acetylated (1.0 mL of dry pyridine, 0.20 mL of Ac₂O, 23°C, N₂, overnight), followed by workup (as described for the steroid of Example 6 [last step]) affording a crude product that was chromatographed (25 g SiO₂, EtOAc). This product was triturated with ether to afford 51 mg (33%) of product as a white solid, m.p. 179-181°C.

Ms (Cl, isobutane): (M + 1) = 450 (M⁺), 432, 391, 371, 348.

25

IR (KBr): 3398 (br), 2932, 2865, 1720 (sh. 1740), 1652, 1538, 1375, 1265, 1236 cm⁻¹.

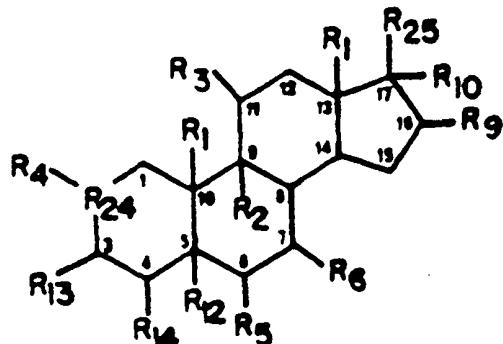
NMR (200 MHz ¹H, CDCl₃): δ 0.89, 1.22, 1.99, 2.17 (all s, 3H); 1.0-2.2 (m); 2.7 (t, J=13, 1H, H-8); 3.03 (s, 1H, OH-17); 4.2 (br s, 1H, H-11); 4.3 (br s, 1H, H-3); 4.96 (AB, J=17.5, Δ v=42, 2H, H-21); 5.8 (d, J=10, 1H, NH).

5 **We Claim:**

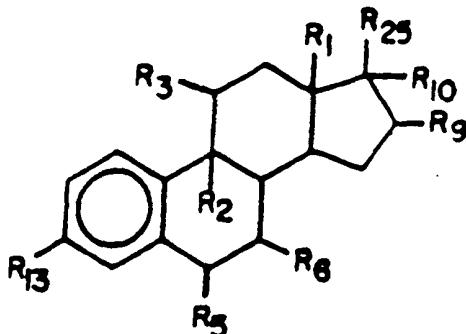
1. A method for treating GLC1A glaucoma which comprises by administering a pharmaceutically effective amount of an angiostatic agent.

10 2. The method of Claim 1 wherein the angiostatic agent has the following structure:

15



20



Structure [A]

Structure [B]

25 wherein R₁ is H, β -CH₃ or β -C₂H₅;

R₂ is F, C₉-C₁₁ double bond, C₉-C₁₁ epoxy, H or Cl;

R₃ is H, OR₂₆, OC(=O)R₂₇, halogen, C₉-C₁₁ double bond, C₉-C₁₁ epoxy, =O, -OH, -O-alkyl(C₁-C₁₂), -OC(=O)alkyl(C₁-C₁₂), -OC(=O)ARYL, -OC(=O)N(R)₂ or -OC(=O)OR₇, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C₁-C₄)alkyl groups, or ARYL is -(CH₂)_f-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C₁-C₃), alkoxy(C₁-C₃), thioalkoxy-(C₁-C₃), Cl₃C-, F₃C-, -NH₂ and -NHCOCH₃ and R is hydrogen, alkyl (C₁-C₄), or phenyl and each R can be the same or different, and R₇ is ARYL as herein defined, or alkyl(C₁-C₁₂);

30 35 R₄ is H, CH₃, Cl or F;

R₅ is H, OH, F, Cl, Br, CH₃, phenyl, vinyl or allyl;

5 R₆ is H or CH₃;

R₉ is CH₂CH₂OR₂₆, CH₂CH₂OC(=O)R₂₇, H, OH, CH₃, F, =CH₂, CH₂C(=O)OR₂₈, OR₂₆, O(C=O)R₂₇ or O(C=O)CH₂(C=O)OR₂₆

R₁₀ is -C≡CH, -CH=CH₂, halogen, CN, N₃, OR₂₆, OC(=O)R₂₇, H, OH, CH₃ or R₁₀ forms a second bond between positions C-16 and C-17;

10 R₁₂ is H or forms a double bond with R₁ or R₁₄;

R₁₃ is halogen, OR₂₆, OC(=O)R₂₇, NH₂, NHR₂₆, NHC(=O)R₂₇, N(R₂₆)₂, NC(=O)R₂₇, N₃, H, -OH, =O, -O-P(=O)(OH)₂, or -O-C(=O)-(CH₂)_tCOOH where t is an integer from 2 to 6;

R₁₄ is H or forms a double bond with R₁₂;

R₁₅ is H, =O or -OH;

15 and R₂₃ with R₁₀ forms a cyclic phosphate;

wherein R₉ and R₁₅ have the meaning defined above;

or wherein R₂₃ is -OH, O-C(=O)-R₁₁, -OP(O)-(OH)₂, or -O-C(=O)-(CH₂)_tCOOH wherein t is an integer from 2 to 6; and R₁₁ is -Y-(CH₂)_n-X-(CH₂)_m-SO₃H, -Y'-(CH₂)_p-X'-(CH₂)_q-NR₁₆R₁₇ or -Z(CH₂)_rQ,

20 wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond, -CON(R₁₈)-, -N(R₁₈)CO-, -O-, -S-, -S(O)-, or -S(O₂)-; R₁₈ is hydrogen or alkyl (C₁-C₄); each of R₁₆ and R₁₇ is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R₁₆ and R₁₇ taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or 25 N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5; Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:

(1) -R₁₉-CH₂COOH wherein R₁₉ is -S-, -S(O)-, -S(O)₂-, -SO₂N(R₂₀)-, or N(R₂₀)SO₂-; and R₂₀ is hydrogen or lower alkyl-(C₁-C₄); with the proviso that the total number of carbon atoms in 30 R₂₀ and (CH₂)_r is not greater than 10; or

(2) -CO-COOH; or

(3) CON(R₂₁)CH(R₂₂)COOH wherein R₂₁ is H and R₂₂ is H, CH₃, -CH₂COOH, -CH₂CH₂COOH, -CH₂OH, -CH₂SH, -CH₂CH₂SCH₃, or -CH₂Ph-OH wherein Ph-OH is p-hydroxyphenyl;

35 or R₂₁ is CH₃ and R₂₂ is H;

or R₂₁ and R₂₂ taken together are -CH₂CH₂CH₂-;

5 or $-N(R_{21})CH(R_{22})COOH$ taken together is $-NHCH_2CONHCH_2COOH$; and pharmaceutically acceptable salts thereof;
with the proviso that if R_{23} is a phosphate, it must form a cyclic phosphate, with R_{10} when R_{13} is = O, except for the compound wherein R_1 is β -CH₃, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is α -F, R_9 is β -CH₃, R_{10} is α -OH, R_{13} and R_{15} are =O and R_{23} is $-OP(O)-(OH)_2$.

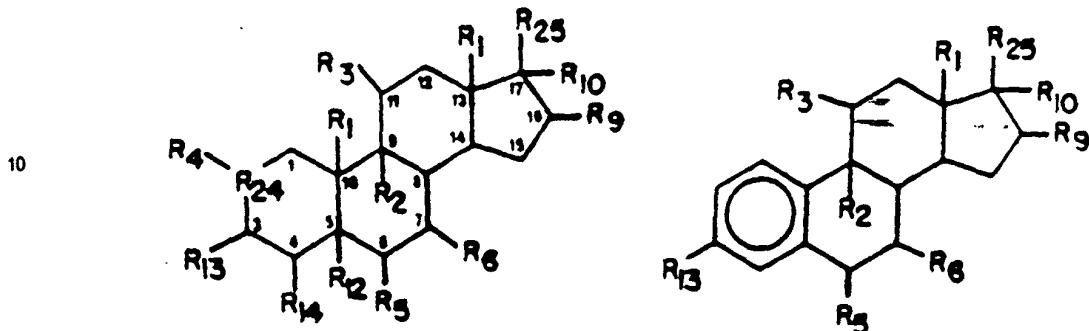
10 R_{24} = C, C₁-C₂ double bond, O;
 R_{25} = C(R_{15})CH₂- R_{23} , OH, OR₂₆, OC(=O)R₂₇, R₂₆, COOH, C(=O)OR₂₆,
CHOHCH₂OH, CHOHCH₂OR₂₆, CHOHCH₂OC(=O)R₂₇, CH₂CH₂OH,
15 CH₂CH₂OR₂₆, CH₂CH₂OC(=O)R₂₇, CH₂CN, CH₂N₃, CH₂NH₂,
CH₂NHR₂₆, CH₂N(R_{26})₂, CH₂OH, CH₂OR₂₆, CH₂O(C=O)R₂₇, CH₂O(P=O)(OH)₂,
CH₂O(P=O)(OR₂₆)₂, CH₂SH, CH₂S-R₂₆, CH₂SC(=O)R₂₇,
CH₂NC(=O)R₂₇, C(=O)CHR₂₈OH, C(=O)CHR₂₈OR₂₆, C(=O)CHR₂₈OC(=O)R₂₇ or
15 R₁₀ and R₂₅ taken together may be =C(R_{28})₂, that is, an optionally
20 alkyl substituted methylene group;
wherein R_{26} = C₁-C₆ (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl);
 R_{27} = R_{26} + OR₂₆; R_{28} = H, C₁-C₆ (alkyl, branched alkyl, cycloalkyl).

3. The method of Claim 2 wherein the compound is selected from the group consisting of
25 21-methyl-5 β -pregnan-3 α ,11 β , 17 α , 21-tetrol-20-one 21-methyl ether; 3 β -azido-21-acetoxy-5 β -pregnan-11 β , 17 α -diol-20-one; 3 β -acetamido-21-acetoxy-5 β -pregnan-11 β , 17 α -diol-20-one; 5 β -pregnan-11 β , 17 α , 21-triol-20-one; 4, 9(11)-pregnadien-17 α ,21-diol-3,20-dione-21-acetate and
4, 9(11)-pregnadien-17 α ,21-diol-3,20-dione.

30 4. The method of Claim 3 wherein the compound is selected from the group consisting of 4, 9(11)-pregnadien-17 α ,21-diol-3,20-dione-21-acetate and 4, 9(11)-pregnadien-17 α ,21-diol-3,20-dione.

35 5. A composition for controlling GLC1A glaucoma comprising a pharmaceutically effective amount of an angiostatic agent.

5 6. The composition of Claim 5 wherein the angiostatic steroid has the following structure:



15

Structure [A]

Structure [B]

wherein R₁ is H, β -CH₃ or β -C₂H₅;

R₂ is F, C₉-C₁₁ double bond, C₉-C₁₁ epoxy, H or Cl;

R₃ is H, OR₂₆, OC(=O)R₂₇, halogen, C₉-C₁₁ double bond, C₉-C₁₁ epoxy, =O, -OH, -O-alkyl(C₁-C₁₂), -OC(=O)alkyl(C₁-C₁₂), -OC(=O)ARYL, -OC(=O)N(R)₂ or -OC(=O)OR₇, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C₁-C₄)alkyl groups, or ARYL is -(CH₂)_f-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C₁-C₃), alkoxy(C₁-C₃), thioalkoxy-(C₁-C₃), Cl₃C-, F₃C-, -NH₂ and -NHCOCH₃ and R is hydrogen, alkyl (C₁-C₄), or phenyl and each R can be the same or different, and R₇ is ARYL as herein defined, or alkyl(C₁-C₁₂);

R₄ is H, CH₃, Cl or F;

R₅ is H, OH, F, Cl, Br, CH₃, phenyl, vinyl or allyl;

R₆ is H or CH₃;

R₉ is CH₂CH₂OR₂₆, CH₂CH₂OC(=O)R₂₇, H, OH, CH₃, F, =CH₂, CH₂C(=O)OR₂₈, OR₂₆, O(C=O)R₂₇ or O(C=O)CH₂(C=O)OR₂₆

R₁₀ is -C≡CH, -CH=CH₂, halogen, CN, N₃, OR₂₆, OC(=O)R₂₇, H, OH, CH₃ or R₁₀ forms a second bond between positions C-16 and C-17;

R₁₂ is H or forms a double bond with R₁ or R₁₄;

R₁₃ is halogen, OR₂₆, OC(=O)R₂₇, NH₂, NHR₂₆, NHC(=O)R₂₇, N(R₂₆)₂, NC(=O)R₂₇, N₃, H, -OH, =O, -O-P(=O)(OH)₂, or -O-C(=O)-(CH₂)_tCOOH where t is an integer from 2 to 6;

5 R₁₄ is H or forms a double bond with R₁₂;
R₁₅ is H, =O or -OH;
and R₂₃ with R₁₀ forms a cyclic phosphate;
wherein R₉ and R₁₅ have the meaning defined above;
or wherein R₂₃ is -OH, -O-C(=O)-R₁₁, -OP(O)-(OH)₂, or -O-C(=O)-(CH₂)_tCOOH wherein t is an
10 integer from 2 to 6; and R₁₁ is -Y-(CH₂)_n-X-(CH₂)_m-SO₃H,
-Y'-(CH₂)_p-X'- (CH₂)_q-NR₁₆R₁₇ or -Z(CH₂)_rQ,
wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond, -CON(R₁₈)-, -
N(R₁₈)CO-, -O-, -S-, -S(O)-, or -S(O₂)-; R₁₈ is hydrogen or alkyl (C₁-C₄); each of R₁₆ and R₁₇ is a
15 lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R₁₆ and
R₁₇ taken together with the nitrogen atom to which each is attached forms a monocyclic
heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or
N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9;
m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;
Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:
20 (1) -R₁₉-CH₂COOH wherein R₁₉ is -S-, -S(O)-, -S(O)₂-, -SO₂N(R₂₀)-, or N(R₂₀)SO₂-; and
R₂₀ is hydrogen or lower alkyl-(C₁-C₄); with the proviso that the total number of carbon atoms in
R₂₀ and (CH₂)_r is not greater than 10; or
(2) -CO-COOH; or
(3) CON(R₂₁)CH(R₂₂)COOH wherein R₂₁ is H and R₂₂ is H, CH₃, -CH₂COOH, -
25 CH₂CH₂COOH, -CH₂OH, -CH₂SH, -CH₂CH₂SCH₃, or
-CH₂Ph-OH wherein Ph-OH is p-hydroxyphenyl;
or R₂₁ is CH₃ and R₂₂ is H;
or R₂₁ and R₂₂ taken together are -CH₂CH₂CH₂;
or -N(R₂₁)CH(R₂₂)COOH taken together is -NHCH₂CONHCH₂COOH; and pharmaceutically
30 acceptable salts thereof;
with the proviso that if R₂₃ is a phosphate, it must form a cyclic phosphate, with R₁₀ when R₁₃ is =
O, except for the compound wherein R₁ is β -CH₃, R₂ and R₃ taken together form a double bond
between positions 9 and 11, R₄ and R₆ are hydrogen, R₁₂ and R₁₄ taken together form a double
bond between positions 4 and 5, R₅ is α -F, R₉ is β -CH₃, R₁₀ is α -OH, R₁₃ and R₁₅ are =O and
35 R₂₃ is -OP(O)-(OH)₂.
R₂₄ = C, C₁-C₂ double bond, O;

5 $R_{25} = C(R_{15})CH_2-R_{23}$, OH, OR_{26} , $OC(=O)R_{27}$, R_{26} , COOH, $C(=O)OR_{26}$,
CHOHCH₂OH, CHOCH₂OR₂₆, CHOCH₂OC(=O)R₂₇, CH₂CH₂OH,
CH₂CH₂OR₂₆, CH₂CH₂OC(=O)R₂₇, CH₂CN, CH₂N₃, CH₂NH₂,
CH₂NHR₂₆, CH₂N(R₂₆)₂, CH₂OH, CH₂OR₂₆, CH₂O(C=O)R₂₇, CH₂O(P=O)(OH)₂,
CH₂O(P=O)(OR₂₆)₂, CH₂SH, CH₂S-R₂₆, CH₂SC(=O)R₂₇,
10 $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OH$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}OC(=O)R_{27}$ or
R₁₀ and R₂₅ taken together may be $=C(R_{28})_2$, that is, an optionally
alkyl substituted methylene group;
wherein $R_{26} = C_1-C_6$ (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl);
R₂₇ = R₂₆ + OR₂₆; R₂₈ = H, C₁-C₆ (alkyl, branched alkyl, cycloalkyl).

15

7. The composition of Claim 6 wherein the angiostatic agent is selected from the group consisting of 21-methyl-5 β -pregnan-3 α ,11 β , 17 α , 21-tetrol-20-one 21-methyl ether; 3 β -azido-21-acetoxy-5 β -pregnan-11 β , 17 α -diol-20-one; 3 β -acetamido-21-acetoxy-5 β -pregnan-11 β , 17 α -diol-20-one; 5 β -pregnan-11 β , 17 α , 21-triol-20-one; 4, 9(11)-pregnadien-17 α ,21-diol-3,20-dione-21-acetate and 4, 9(11)-pregnadien-17 α ,21-diol-3,20-dione.

8. The composition of Claim 6 wherein the compound is present at a concentration between 0.005 and 5.0 weight percent.

25 9. The composition of Claim 7 wherein the compound is 4, 9(11)-pregnadien-17 α ,21-diol-3,20-dione-21-acetate or 4, 9(11)-pregnadien-17 α ,21-diol-3,20-dione.

10. The composition of Claim 8 wherein the compound is present at a concentration of between 0.05 and 2.0 weight percent.

30

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/25913

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/57 A61K31/575 A61K31/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | WO 91 19731 A (UPJOHN CO) 26 December 1991 see page 4, line 31 see page 15 --- | 1-10 |
| X | US 5 371 078 A (CLARK ABBOT F ET AL) 6 December 1994 see column 2, line 38 - line 41 see column 3; figures A,B --- | 1-10 |
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| X | US 5 698 545 A (CLARK ABBOT F ET AL) 16 December 1997 cited in the application see claims 1-3 --- | 1-10 |
| | | -/- |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 May 1999

Date of mailing of the international search report

25/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL-2200 LM The Hague

Authorized officer

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 98/25913

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/25913

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: _____
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the compounds mentioned in the examples of the description.
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.: _____
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: _____

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanying the payment of additional fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No
PCT/US 98/25913

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No.

PCT/US 98/25913

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